



Update of Vulvovaginal Candidiasis in Pregnant and Non-pregnant Patients

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Abstract

Purpose of the Review *Candida albicans* vulvovaginitis is one of the most frequent symptomatic infections in women and its incidence increases in reproductive age and pregnancy. Currently there are more specific and sensitive tests to identify *Candida* species that are resistant to antifungal agents, such as PCR and MALDI TOF MS, in order to improve prognosis.

Recent Findings The genus *Candida* is part of the microbiota in humans; however, many species can become pathogenic. Vulvovaginitis caused by non-*albicans Candida* are becoming very important due to their high levels of antifungal resistance, which makes treatment difficult. Therefore, in addition to using phenotypic, biochemical tests, molecular analyses should be used to improve diagnosis and give appropriate treatment.

Summary Both in childhood and in reproductive age, women are exposed to several episodes of vulvovaginitis, mainly due to bacteria and fungi, due to various risk factors. Among the fungi, the most common agent is *Candida albicans* and within the non-*albicans* is *Candida glabrata*, but there are other species related to greater resistance and recurrence.

Keywords Vulvovaginal candidiasis · *Candida albicans* · Non-*albicans Candida* species · *Candida glabrata* · Antifungal drugs

Introduction

Vulvovaginitis (VV) is a common pathology during the reproductive age, caused by bacteria (40–50%), fungi (20–25%),

sexually transmitted diseases (15–20%) and non-infectious origin (5–10%) [1, 2, 3, 4, 5].

In women, there is a balance between *Candida*, the vaginal microbiota and the immune defense mechanisms; and whenever an element is altered, the fungus takes advantage and causes infection [3].

Currently, vulvovaginitis caused by *Candida* (VVC) is a problem ignored by health care personnel or is perceived as an insignificant pathology in women [3], even when it is one of the main causes of medical consultation and acquisition of over-the-counter medicines [3, 6].

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Definition

VV is a disorder of the vulva and/or vagina caused by infection, inflammation, or changes in the microbiota [1, 2]. VVC is one of the most common opportunistic fungal infections of the female genital tract, caused by the species of the genus *Candida* [3, 7, 8, 9].

Epidemiology

At a global level, VVC is the most frequent symptomatic infection in women of reproductive age. It is the second most common cause of VV in the USA and the first in Europe [3•, 6]. The prevalence of infection caused by *Candida* is approximately of 20% (range of 10–55%) of all VV [3•]. Around 70–75% of all women experience at least once a vaginal infection caused by fungus and between 7 and 50% present recurrences [5•, 9, 10, 11•]. Between 10 and 40% of women are asymptomatic carriers [2•, 3•, 7•, 8•, 12, 13•].

Etiology

Candida spp. are commensal fungi that form part of the microbiota in the human being, being present in 10–20% of the lower genital tract of healthy women of reproductive age [11•].

Various studies around the world reveal that *C. albicans* is the principal agent of the VV caused by fungi (85–95 %) [8•, 14•] and of the infections caused by non-*albicans Candida*, those of the *Candida glabrata* complex (*Candida glabrata sensu stricto*, *Candida nivariensis*, and *Candida bracariensis*) and *Candida tropicalis* are the most frequent ones, although other species have been found such as *Candida parapsilosis sensu stricto*, *Candida krusei*, and *Candida guilliermondii* (emergent) [2•, 3•, 7•, 9, 11•, 13•, 14•, 15].

Previously, *C. glabrata* was considered avirulent as it is part of the microbiota of the skin and mucous membranes; however, the indiscriminate use of antibiotics and immunosuppressants have favored infections caused by this species [11•].

A study performed in Sarajevo (2006) identified the etiology of the VVC in pregnant women (203 patients) and non-pregnant women (244 patients) in an age range of 20–38 years. Microscopic examinations and vaginal cultures were performed, finding a positive culture in 46% of pregnant women, identifying *C. albicans* (87.4%), *C. glabrata* (4.2%), *C. krusei* (3.2%), *C. tropicalis* (2.1%), *C. parapsilosis* (2.1%), and *C. guilliermondii* (1.1%). On the other hand, in non-pregnant women, 25.4% of them presented a positive culture, being *C. albicans* (90.3%) the most common agent, followed by *C. glabrata* (3.2%), *C. parapsilosis* (3.2%), *C. krusei* (1.6%), *C. tropicalis* (1.6%) [3•].

The pathogenicity of *Candida* spp. varies according to the species. It has been observed that *C. albicans* is more virulent than *C. krusei* but it is more susceptible to antifungal medications [11•].

Risk Factors

Age is one of the main risk factors for VV, being the pediatric stage the most vulnerable due to the smaller amount of estrogen, which makes the vaginal epithelium thinner and with the least amount of lactobacilli, with a neutral pH, favoring the development of some microorganisms [2•].

Some authors report that the VVC is rare in children and in the postmenopause due to the estrogen deficiency [6]. When it comes to girls, the proximity of the anus with the vulva increases the susceptibility of VVC, since the rectum is the main reservoir for *Candida* [2•, 13•].

Sexual activity increases the incidence of VVC, although there are no studies found to report conclusively that it is indeed sexually transmitted [8•, 11•].

Other risk factors to VVC are: oral contraceptives with a high estrogen content, glucocorticoids, antibiotics, chemotherapy, hot and humid climates, care in clinics of sexually transmitted diseases, comorbidities that cause immunosuppression and idiopathic [3•, 5•, 7•, 8•, 9, 11•, 13•, 14•, 15].

In poorly controlled diabetes, VVC is a common problem with a ratio of 2:1 compared with non-diabetic women (due to hyperglycemia and immunosuppression) [15].

The cause of recurrent VVC (RVVC) is multivariate and the mechanisms of resistance to antifungal medications are not well known. Some authors suggest a genetic predisposition of the patient, so the polymorphisms are a risk factor for women to develop VVC and RVVC [7•].

VVC has been found in pregnant women between 30 and 40%. During pregnancy, there is an increase of hormone secretion which alters the vaginal microbiota, increasing the risk of infections. High levels of estrogen cause an increase in the amount of glycogen in the vagina and provide a good source of carbon which is necessary for the growth of *Candida* and its germination [3•, 16•, 17•].

Pathophysiology

The presence of *Candida* spp. (in vagina) is regulated by *Lactobacillus*, which produce antimicrobial compounds such as hydrogen peroxide, lactic acid, and bacteriocins. In addition, they compete to establish on adhesion sites in the vaginal epithelium, so that changes which alter the balance of the microbiota favor the development of infection [18, 19, 20].

Experimental evidence shows that *Candida* spp. can regulate its genes in a process of adaptation to the environment that it colonizes, and exhibit a particular profile of virulence factors according to the site that it infects (oral, gastric, or vaginal mucosa) [21•].

The transition from yeast to hypha, which is the filamentous form responsible for the invasion, damage to tissues and organs, is considered to be the major virulence factor of

C. albicans. This transition depends on a complex network of elements that detect changes in the microenvironment and regulate transcription factors that encode the formation of hyphae, production of adhesins, hydrolytic enzymes, and factors associated with the formation of biofilm, which is a structure that contains yeast, pseudohyphae, and hyphae, surrounded by an extracellular matrix. Its development is divided into four stages: adherence, initiation or proliferation, maturation, and dispersion [22, 23••, 24•, 25]. The virulence of *Candida* spp. and its resistance to treatment is due to the formation of a biofilm [11••].

The overexpression of transcription factors related to the formation of biofilms of *Candida* spp. are responsible for the maintenance of the different morphotypes, such as NRG1 (yeast) and UME6 (hyphae), corroborating the importance of morphogenetic changes in the activation of the immune mechanisms involved in the pathogenesis of infection and showing the relevance of the transition from yeast to hyphae as an important virulence factor in VVC [23••].

Characteristics of *Candida* spp. that increase its pathogenicity with the formation of biofilm:

- The growth of the fungus embedded in a matrix rich in exopolysaccharides makes the penetration of the antifungal agents difficult, which gives resistance.
- The interaction between the fungus and the epithelial cell (EC) is modified, which prevents the recognition and activation of the host's innate mechanisms of inflammatory response.
- Makes inefficient the immune defense mechanisms and evades the host response.

The formation of biofilm on the vaginal mucosa has been observed on in vivo models, ex vivo vaginal tissue, and in vitro cultures of EC and fungus lines [26••].

Phases of the formation of biofilms of *Candida* spp. in vitro (main features and duration) [27•, 28].

- Initial: formation of microcolonies — 11 h.
- Intermediate: production of extracellular polymeric substances (EPS), a bilayer of yeast, germinal tubes and/or young hyphae — 12 to 30 h
- Maturation: development of a thick layer of EPS where yeasts and hyphae form a dense net — 38 to 72 hours.
- Dispersion: mature biofilms release non-adherent daughter cells (yeast), to spread the colonization and infection.

When the biofilm is formed, it has mechanisms of resistance such as: incomplete penetrance of antibiotics and immune cells of the host through the matrix, physiological changes in the microenvironment due to nutrition responses and low growth, phenotypic changes, perception of quorum among microorganisms, expression of efflux pumps that can

carry antimicrobial agents outside of the cells and the presence of “persistent” cells [11••].

Among the virulence factors of *Candida* spp., the production and regulation of hydrolytic enzymes as well as the mechanisms by which they exercise their function have been object of study, such as the secretory aspartyl proteases (SAP), which are a group of exoenzymes (Sap 12–Sap 10) that perform multiple roles in VVC and whose expression can be regulated by changes in pH, a morphotype determined and the stage of the infectious process. Another mechanism described is the activation of the inflammasome NLRP3 (NOD-like receptor Pyrin domain containing) in the host, that is essential for the production of IL-1 β , which is key cytokine in the pathogenesis of *Candida* [24•, 26••, 29, 30, 31].

There are mechanisms of innate immunity in the female genital tract that are important in the maintenance of the immune surveillance against microorganisms, the commensalism, and the protection during the invasion. It has been demonstrated that populations of polymorphonuclears (PMN), macrophages, dendritic cells, NK cells, $\gamma\delta$ T cells, and innate lymphoid cells (ILC) may be resident or be recruited in response to local stimuli; its mechanism of action may result in the death of the fungus in a direct manner or through immune mediators (indirectly). The cells of the innate immunity produce reactive oxygen species (ROS), such as hydrogen peroxide and superoxide, to kill pathogens. These ROS cause oxidative stress to *C. albicans* and induce irreversible damage, causing apoptosis through the formation of protein-protein cross-links or interacting with lipids and nucleic acids. As a response, *C. albicans* and *C. glabrata*, express several antioxidant genes to protect from the oxidative stress, such as catalase (CAT1), which stimulates the degradation of hydrogen peroxide (H₂O₂) in water (H₂O) and oxygen (O₂), the glutathione peroxidase (GPX) and superoxide dismutase (SOD), which are enzymes that capture peroxide. The expression of the genes encoding these proteins is critical for the virulence and pathogenesis of both [26••, 32, 33•].

Another element that is involved are the EC as they produce a broad spectrum of antimicrobial peptides present on the surfaces of the mucous membranes and that respond quickly to inflammatory or pathogenic stimuli. Also, the secretion of soluble mediators (alarmines, antimicrobial peptides, chemokines, and cytokines such as IL-1, IL-6, IL-8, and TNF- α), actively participate in the initial phase of the response and recruit another cell population [2••, 11••].

The EC have the ability to discriminate between the saprophytic form of *C. albicans* and its transition to the hyphal phase, so that the yeast morphotype is tolerated and the emission of the pseudohyphae is considered an alert signal, initiating the local inflammatory response. Both the release of alarmines and IL-8 favor the infiltrate of PMN and contribute to the onset of symptoms, that is to say, the vaginal colonization is asymptomatic and occurs in the absence of

inflammatory response, while the symptomatic form is accompanied by an abundant PMN infiltration. Therefore, the susceptibility to infection is associated with an aggressive inflammatory response, while resistance is associated with the activation of an anti-inflammatory profile [11••].

The EC is fundamental in the host response to *C. albicans* as it recognizes both yeast pseudohyphae and hyphae. Only the hyphae can invade the EC by induced endocytosis and/or active penetration, causing the activation of the EC. The endocytosis of *C. albicans* is mediated by multiple epithelial receptors and the fungal invasion Als3, but the EC are activated primarily by the peptide toxin candidalysine associated to the hyphae. The candidalysine deteriorates the epithelial membranes and activates the damage response pathways mediated through p38/cFos and ERK/MKP1, which causes the immune activation and secretion of cytokines and chemokines. These effector molecules recruit innate immune cells such as neutrophils, macrophages, and innate cells type 17. The neutrophils and macrophages kill or restrict directly the fungus through mechanisms of phagocytosis and/or formation of extracellular traps of neutrophils and the innate cells type 17 secrete IL-17 and other inflammatory effectors to recruit even more neutrophils and promote the barrier function in the mucosa. This innate immune response works in conjunction with the EC to control the infection by fungi. It is clear that the formation of hyphae is critical for both the pathogenicity of *C. albicans* and the host response [34, 35].

With regard to the recognition of the pathogen-associated molecular patterns (PAMP) of *Candida*, there are three families of pattern recognition receptors (PRR), which are associated, coupled, and abound in the activation pathways. In the family of the C-type lectin receptors (CLR), the most studied one is the dectin-1, which has the β -glucans from the wall of the fungus as a ligand, the rest of the receptors of the family (mannose, dectin-2, DC-SIGN, mincle, and others) recognize glucidic structures such as mannose and fucose present in the wall of *Candida* [36, 37].

Toll-like receptors (TLRS) were the first PRR identified in mammals. Of them, TLR2 recognizes phospholipomannan, TLR4 structures rich in O-mannosides, TLR7 the RNA of the fungus, and TLR9 the DNA of *Candida* [11••].

From the NOD-like receptors (NLR), the NLRP3 is expressed in macrophages, monocytes, dendritic cells, and EC and are involved in the production of IL-1 β , so they are important in the antifungal immune response [38].

Within the adaptive immunity, T/NK cells, $\gamma\delta$ T lymphocytes, and the ILC3, produce copious amounts of IL-17 involved in the defense of the mucosa [35].

Within the genetic mutations associated with greater susceptibility of *Candida* infections, we find errors which affect

the receptors of the innate immunity such as the dectin-1 molecule and its adaptor protein (CARD9), in chronic mucocutaneous candidiasis and RVVC. Isolated mutations in TLR2, polymorphisms in the NLRP3 gene, and the polarization of the macrophages to profile M2 are associated with greater susceptibility to RVVC. Mutations in the gene STAT-1 (signal transducer and activator of transcription 1), defects in the IL-17 receptor, and IL-17 deficiency are important in the immune response of the mucosa against *C. albicans* [11••, 39].

During pregnancy, the vagina is more prone to various opportunistic infections such as VVC and infection caused by *Trichomonas vaginalis* (TV) as a result of hormonal changes (increased levels of estrogen, progesterone, and the production of glycogen), changes in pH, composition, and proportion of the vaginal microbiota, as well as the immunosuppression [40, 41•].

Clinical Picture

The vaginal signs and symptoms have an impact on the quality of life, that's why they are one of the most common causes of gynecological consultation.

VVC can be classified as: non-complicated when they occur infrequently, in immunocompetent patients and are caused by *C. albicans* and complicated when they are recurrent, occur in immunosuppressed patients and are caused by *Candida* non-albicans species [2••, 4••, 5•, 9, 14•]. The non-complicated form is the most common one and is characterized by itching, vaginal pain, vulvar burning sensation, dyspareunia, dysuria, and mildly unpleasant odor. Upon exploration there is erythema and vulvar edema, fissures, papulopustular injuries, white-yellowish plaques on the walls of the vagina and cervix, vaginal fluid (aqueous or lumpy and thick—consistency of cottage cheese), which can help in the differential diagnosis of other VV (Table 1); the clinical picture is often exacerbated during the week prior to menstruation [31, 42••].

RVVC in addition to complying with the criteria of presenting at least four episodes a year, symptomatic and documented, with resolution of symptoms between episodes, can also be associated with an adequate response to antifungal therapy (even if incomplete) and exacerbation of symptoms with the use of antibiotics [1•, 5•, 43, 44].

In pregnancy, the presence of vaginitis is related to abortion, intrauterine infection, fetal growth retardation, premature rupture of membranes, preterm birth, low birth weight, puerperal infection, and other adverse pregnancy outcomes. The diseases that progress rapidly or increase their severity can cause cervical cancer and other diseases, which has an adverse impact on the maternal-fetal health [41•].

Table 1 Most common signs and symptoms of vaginitis

Diagnosis	Etiology	Symptoms	Type of discharge	Signs	Other risks
Bacterial vaginosis	Anaerobic bacteria (<i>Prevotella</i> , <i>Mobiluncus</i> , <i>Gardnerella vaginalis</i> , <i>Ureaplasma</i> , <i>Mycoplasma</i>)	Fishy odor in the vagina, with or without pelvic discomfort	Thin and homogeneous secretion, which may worsen after intercourse, with “fishy” odor	Without inflammation	Greater risk of HIV infection, gonorrhea, chlamydia and herpes
Vulvovaginal candidiasis	Specieses of the genus <i>Candida</i>	Vulvar itching or burning; without a characteristic odor	White discharge, watery or thick and clumped (like cottage cheese)	Vulvar edema and erythema	–
Trichomoniasis	<i>Trichomonas vaginalis</i>	Pain or vaginal pain	Green or yellow discharge, frothy, with bad smell	Inflammation; cervix with strawberry aspect	Increased risk of HIV infection Greater risk of preterm labor Must be examined for other sexually transmitted infections
Atrophic vaginitis	Estrogen deficiency	Vaginal dryness, dyspareunia, itching	Clear and thin discharge	Inflammation; vaginal mucosa friable and thin	–
Allergic vaginitis/irritating	Contact irritation or allergic reaction	Burning, pain	–	Vulvar erythema	–
Inflammatory vaginitis	Possibly autoimmune	Burning, dyspareunia	Purulent flow	Vaginal atrophy and inflammation	Associated with low estrogen levels

HIV human immunodeficiency virus

Reference: [5•]

Diagnosis

The clinical history is not enough to make the differential diagnosis of VVC. It is essential to perform the exploration, laboratory tests, and/or fresh examination with KOH (during the consultation) to determine the diagnosis.

In the pelvic examination, inflammation is evident, the cervix is usually not inflamed and there is no abnormal discharge through the cervical os. Laboratory studies include: (1) microscopic examination of fresh vaginal exudate with KOH (10–40%), where blastoconidia or pseudohyphae can be observed which suggest infection caused by non-albicans *Candida* or *C. albicans*, respectively [45]. (2) The pH < 4.5 in vaginal samples is a sensitive test that guides the diagnosis of VVC, considering the fact that at pH 4.5 *C. albicans* presents greater production of phospholipases, which are its main factor of pathogenicity [46]. (3) The cultivation is the “gold standard” to demonstrate the presence of *Candida*, but the presence does not necessarily indicate infection but the quantity and morphology of the isolated yeasts [47, 48]. The quantification of *Candida* is determined with the levels of antigen using the latex agglutination test, which yields results in 3 min, with adequate specificity, sensitivity, and diagnostic efficiency (> 80%) [52]. It is necessary to identify the yeast at a species level, particularly in patients with RVVC, as this influences the selection and duration of treatment [45, 49••, 50•]. To identify the species, cultures are performed in chromogenic media (CHROMAgar *Candida*, ChromID *candida* agar) [48] and biochemical tests, for which there are multiple systems available commercially (API ID 32C, Rapid ID yeast PLUS, API 20 C, Vitek2, Yeast Star, Yeast Plus system, Auxacolor and API *Candida*). All these tests require time and the results are not always clear, especially when it comes to rare species or closely related ones, such as: *C. dubliniensis*, *C. africana*, and *C. albicans*, or *C. glabrata*, *C. bracarensis* and *C. nivariensis* [45, 51•, 52]. These problems are resolved with the implementation of molecular tests (which allow the characterization of yeasts isolated in culture or directly in vaginal fluid), among which stand out the hybridization with DNA probe (Affirm™ VPIII, Becton, Dickinson and Company) that detects *Candida* with high sensitivity and specificity (> 80.0%) when compared with the culture. It has the advantage that the doctor can perform the test during the gynecological consultation [53••]. PCR amplification of the D1/D2 regions of the 26S rRNA or internal transcribed spacer (ITS) constitutes the molecular test most used because it offers greater accuracy, specificity, sensitivity, and speed in the identification of *Candida* spp. [6, 47, 54••, 55]. The PCR also serves to detect specific mutations in genes associated with resistance to treatment, such as ERG11-2 (resistance to azoles) [56•], as well as for the genotypification of isolates of the same species, which is of interest in epidemiological studies [45, 57••, 58••, 59••]. Recently, matrix-assisted laser-desorption and

Table 2 Causes of vulvovaginitis during childhood, adolescence and adult women

Stage	Cause of vulvovaginitis	
	Infectious	Non-infectious
Children	Bacterial vulvovaginitis	Non-specific vulvovaginitis Lichen sclerosus Labial adhesion
	Nematodes (ascariasis, oxyuriasis)	Foreign body Dermatosis (eczema, psoriasis, others)
Adolescence	Yeast infection	Physiological secretion
	Bacterial Vaginosis	Dermatosis
	Sexually transmitted infection	
Mature	Bacterial vaginosis	Atrophic vaginitis Desquamative inflammatory vaginitis Vulvar vestibulitis
	<i>Candida</i> infection	Erosive lichen planus Pemphigus vulgaris
	Trichomoniasis	Pharmacodermia (SJS and TEN) Pemphigus mucomembranous
	Herpes simplex	Pemphigus vulgaris
		Malignant (extramammary Paget's disease and squamous-cell carcinoma)

SJS = Stevens-Johnson Syndrome; TEN = toxic epidermal necrosis

Reference: [2••, 4••, 21•, 61]

ionization time-of-flight mass spectrometry (MALDI-TOF MS) has shown good results in the identification of *Candida*, based on a broad spectrum of proteins [60•]. These tests are not available in clinical laboratories of low-income countries [51•].

Differential Diagnosis

In the reproductive age, symptoms are caused frequently by local infection. In other stages (childhood, adolescence, and menopause) another etiology is considered (Table 2), such as: allergic contact dermatitis, vaginal atrophy, or parasitic infection [8•].

In childhood, foreign bodies in the vagina and sexual abuse must be considered. A retrospective review of 15-year-old prepubescent girls who presented recurrent vaginal flow showed that sexual abuse might have been involved in 5% of cases. On the other hand, this age group is more exposed to multiple risk factors that increase the susceptibility of VV [2••].

During adolescence, the etiology and treatment are different from the previous stage, because there are changes in the vaginal microbiota (greater presence of lactobacilli) and a more acidic pH, which provides a protective environment against infections. During this stage, the most frequent causes

of infection are nonspecific vaginitis, yeast infections, bacterial vaginosis, and sexually transmitted infections [2••].

Abundant vaginal discharge may occur in healthy women. This situation constitutes a diagnosis of exclusion, which is important to recognize in order to calm the patient's anxiety and to avoid unnecessary treatment [4••].

After menopause, there is a significant decrease in the barrier function of the skin and in the immunity, and vulvovaginal tissues are particularly susceptible to these changes. In all stages of life, the vulva and the vagina are more sensitive to a wide range of irritants and allergens in comparison to other sites of the skin and these increase after menopause with tissue atrophy and deterioration of the immune system. Histological, chemical, and immunological changes that occur with the cease of the hormonal function and aging increase the risks for the vulvovaginal health, being the vaginal atrophy, lichen (sclerosus and atrophic) and the VVC being the most common [61, 62, 63].

Treatment

The pharmacological treatment for VVC is indicated only when it is symptomatic, despite the growth of the yeast in the culture, or its identification through another method [13••].

The uncomplicated cases can be managed with topical over the counter medications or oral antifungals for 1 to 7 days,

Table 3 Treatment for vulvovaginitis caused by *Candida*

Type of vulvovaginitis	Treatment			Reference
	Drug	Route of administration	Dose	
Uncomplicated VVC	Fluconazole 150 mg	Oral	Single dose	[5•, 13•••]
	Clotrimazole 1% cream	Intravaginal route	5 g a day, 7 to 14 days	[5•]
	Clotrimazole 2% cream	Intravaginal route	5 g per day, for 3 days	
	Miconazole 2% cream	Intravaginal route	5 g per day, for 7 days	
	Miconazole 4% cream	Intravaginal route	5 g per day, for 3 days	
	Miconazole 100 mg	Vaginal ovule	An ovule a day, for 7 days	
	Miconazole 200 mg	Vaginal ovule	An ovule a day for 3 days	
	Miconazole 1200 mg	Vaginal ovule	An ovule, single dose	
	Tioconazole ointment 6.5%	Intravaginal	5 g in a single dose.	
	Butoconazole cream 2%	Intravaginal	5 g in a single dose	
	Terconazole cream 0.4%	Intravaginal	5 g per day, for 7 days	
	Terconazole cream 0.8%	Intravaginal	5 g a day for 3 days	
	Terconazole 80 mg	Vaginal ovule	One ovule per day, for 3 days	
VVC by <i>C. albicans</i> , recurrent	Fluconazole 150 mg	Oral	Initial dose: One capsule every three days, for three doses Maintenance dose: One capsule every week for 6 months	[4••, 5•, 14•]
Complicated VVC or non- <i>albicans</i>	Boric acid 300–600 mg	Vaginal ovule	An ovule at night, for 14 to 21 days	[4••, 13••]
	Flucytosine cream 15.5%	Intravaginal	5 g a day for 14 days	
	Amphotericin B 50 mg	Vaginal ovule	One ovule a day, for 14 days	
	Nystatin 100,000 units	Vaginal ovule	One ovule per day, for 3 to 6 months	[13••]
	Itraconazole 100 mg	Oral	Two capsules in single dose	[44]
VVC in pregnancy	Topical azoles (Imidazole) for 14 days			[13••]

however, some antifungal medications are not effective against infections caused by non-*albicans Candida* [4••]. The first-line treatment for uncomplicated VVC is topic (azoles) or fluconazole (150 mg orally, single dose) (Table 3) [5•, 14•].

In immunocompromised, diabetic women who do not respond to standard treatment, a vaginal culture for *C. albicans* has to be performed. If the result is positive, treatment with oral fluconazole 150 mg every 3 days for three doses could be given. For RVVC cases, the initial treatment must be continued with maintenance therapy with oral fluconazole 150 mg per week for 6 months [4••, 14•].

The *Candida* non-*albicans* infections may be resistant to azoles, for example, patients with *C. glabrata* are 50% resistant to this type of drugs [8•], so the susceptibility of the agent must be confirmed by means of an antifungal susceptibility testing [4••]. Some authors report a successful treatment for non-*albicans Candida* using vaginal boric acid (300 to 600 mg a day for 14 to 21 days), flucytosine in vaginal cream 15.5% intravaginal (5 g during 14 days), amphotericin B vaginal ovules (50 mg for 14 days), nystatin ovule (100,000 units once a day for 3 to 6 months) or

Itraconazole capsules 100 mg (400 mg orally single dose), which has been observed in clinical practice to be very effective against *C. glabrata*. Despite the existence of various treatments against the VVC non-*albicans*, boric acid, itraconazole, and nystatin are the ones with greater access, due to them being more commercial, unlike the vaginal ovules of flucytosine or amphotericin B, which are usually prepared by a pharmacist [4••, 13••].

In pregnant women, symptoms can be more intense and severe, so the treatment also tends to be more prolonged. The use of oral fluconazole must be avoided, due to the teratogenic effects in the first quarter, such as tetralogy of Fallot, so management with topic azoles is the only recommendation, being able to use imidazole external creams or intravaginal ovules for 14 days. The intravaginal boric acid has been associated with a double risk of birth defects when used in the first trimester of pregnancy [13••].

The resolution rates of VVC with proper treatment can be measured in the short term (5–15 days) or medium term (3–6 weeks), with the absence of the symptoms, despite a positive culture, due to the fact that *Candida* is part of the vaginal microbiota [8•].

Conclusion

The diagnosis of the VVC is complicated due to the fact that *Candida* spp. is part of the vaginal microbiota, therefore, it is important to use all the available tools to make safe the treatment during pregnancy and avoid mistakes that could lead to ineffective or unnecessary treatment.

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Compliance with ethical standards

Conflict of Interest Tito Ramírez-Lozada, Victor Manuel Espinosa-Hernandez, María Guadalupe Frias-De-León, and Erick Martínez-Herrera declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

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